

ORAL GLUCOSE TOLERANCE TEST

1.1 Background and Rationale

Diabetes is a major public health problem in old age, particularly for older African-Americans, and the incidence of diabetes appears to be increasing. About 50 percent of older Americans are likely to have glucose intolerance or diabetes, making this risk factor almost as common as hypertension. Both the risk factors for diabetes and glucose intolerance and the sequelae are relatively understudied in old age and may contribute not only to cardiovascular disease but to other conditions such as decline in pulmonary function or osteoarthritis that involve changes in collagen. Advanced glycosylation products may contribute to chronic inflammation.

Poorly controlled diabetes may increase weight loss in older persons. Little is known as to whether diabetes and glucose intolerance contribute to decline in functional status, independently from other weight-related health conditions.

High body mass index increases the risk of glucose intolerance; conversely, among the elderly, loss in muscle mass may increase the risk of glucose intolerance. Increased intra-abdominal fat increases the risk of diabetes and glucose intolerance in younger persons.

To identify diabetics only, a fasting glucose and a glycosylated hemoglobin test could be used. However, to describe the range of glycemia in the population and to identify those who may be insulin resistant, it is necessary to carry out an oral glucose tolerance test. Between 50 and 80% of elderly persons with abnormal glucose tolerance are asymptomatic. In population surveys, approximately 50% of diabetics and almost all participants with impaired glucose tolerance will not have been previously diagnosed. Although the fasting glucose measurement will identify some diabetics, this measurement alone will miss approximately 50% of participants with abnormal glucose tolerance.

1.2 Definitions

Diabetes: A metabolic disease characterized by abnormally high blood sugar and increased risk of several chronic complications including heart, vascular, eye, and kidney disease. Many with this disease are asymptomatic but remain at increased risk of complications. In population studies, the standard criterion for diagnosis is an oral glucose tolerance test.

Impaired glucose tolerance: Abnormal glucose tolerance level between normal and diabetes. These persons appear to have an increased risk of cardiovascular disease, but little or no increased risk of eye and kidney disease. They are at high risk for further deterioration of glucose tolerance to diabetes. An oral glucose tolerance test is required to diagnose impaired glucose tolerance.

Oral glucose tolerance test (OGTT): A standardized test for the diagnosis of diabetes and other abnormalities of glucose tolerance. It has several forms. The simplest, or survey OGTT recommended by the World Health Organization for diabetic screening, consists of a fasting blood sample, consumption of a standard drink containing 75 g glucose, and a second blood test two hours after the start of drink consumption.

Hypoglycemic medication: Medications that lower blood sugar. There are two classes: insulin, which is administered by injection, and oral hypoglycemics.

Oral hypoglycemics:

<u>Generic Name</u>	<u>Trade Name</u>
Tolbutamide	Orinase
Acetohexamide	Dymelor
Tolazamide	Tolinase
Chloropropamide	Diabinese
Glipizide	Glucotrol
Glyburide	Diabeta, Micronase
Metformin	Glucophage
Acarbose	Precose
Glicazide	Diamicron
Glimepride	Amaryl
Troglitazone	Rezulin

Fasting: Abstinence from all food and drink (except water and prescription medications) for 12 hours prior to the clinic visit; 8 hours is the absolute minimum.

Insulin-requiring diabetics: Persons who use insulin injections to control blood glucose (sugar). Many older persons are insulin requiring but not dependent.

Insulin-dependent diabetics: Persons whose pancreas produces little or no insulin and require insulin injections to prevent development of diabetic ketoacidosis.

Non-insulin-dependent diabetics: Persons who do not require insulin to prevent diabetic ketoacidosis. Persons may take insulin. Most elderly persons taking insulin will have this form.

2. Equipment and Supplies

- Standard 75 g glucose drink
- Supplies for blood draw (see Chapter 3B, Blood and Urine Collection, Section 2. Equipment and Supplies)

3. Safety Issues and Exclusions

Although the glucose tolerance test could be performed safely to all Health ABC participants, data obtained from diabetics taking insulin or oral hypoglycemic drugs would be difficult to interpret. Therefore, this test will be omitted in these participants.

3.1 Exclusions

- Diabetics treated with insulin or oral hypoglycemics. Known diabetics treated by diet alone will be tested.
- Participants who do not observe the overnight fast (abstinence from all food and drink, except water and prescription medication, is requested for 12 hours). This includes abstinence from coffee, tea, and soft drinks. Participants who do not fast for the absolute minimum of 8 hours are excluded from the oral glucose tolerance test. Non-fasting participants, however, will have blood drawn even though they will not be given the glucose. Non-fasting participants will be asked if they would be willing to return fasting at a later date.
- Participants from whom no blood draw is obtained.
- If a participant is not administered the oral glucose tolerance test, an OGTT form must still be filled out through question 2. In addition, you must put an X in the box labeled N/A next to cryovial 46 on the Laboratory Processing form (see Lab Specimen Processing chapter).

3.2 Procedures for Diabetics

1) Diabetic status will be determined by self report on the baseline home visit questionnaire. Diabetic status will be verified with participant at the time the clinic visit is scheduled, and during the phone reminder call.

2) The following instructions are given to diabetics at scheduling of the clinic visit:

- Diet-controlled diabetics are instructed to fast overnight.
- Diabetics taking oral hypoglycemic medications are instructed to fast overnight (unless a bedtime snack was prescribed by their physician) and to come to the clinic without taking their morning oral hypoglycemic medication. The morning medication dose should be brought to the clinic.
- Insulin-requiring diabetics are instructed to fast overnight (unless a bedtime snack was prescribed by their physician) and to come to the clinic without taking their morning insulin. The morning insulin dose should be brought to the clinic.

3) The presence of previously diagnosed diabetes and whether hypoglycemic medications (oral hypoglycemics or injected insulin) are taken will be verified prior to the OGTT using questions on the exam form.

4) Insulin-dependent and oral hypoglycemic-dependent participants:

- The OGTT is not done on insulin-dependent or oral hypoglycemic-dependent diabetics. *If the participant takes insulin, put an X in the box labeled N/A next to cryovial 26 on the Laboratory Processing form*. No assay for fasting serum insulin will be performed in these participants.
- Fasting blood samples should be drawn promptly after the ECG examination.
- All known diabetics taking insulin or oral hypoglycemic medications should be scheduled for the clinic visit before 10 am or as determined by the participant's usual routine.
- The participant should take their usual diabetic medication immediately following the fasting blood draw, and have a snack provided by the Field Center. This snack must be provided promptly (within 10 minutes) after the diabetic medication is taken.

5) Diabetic participants not taking hypoglycemic medications will be treated exactly like all other HABC participants.

3.3 Potential Problems in Diabetic Participants:

An additional consideration is the possibility that diabetic participants will develop low blood sugar or an "insulin reaction". The best protection against this is to be certain that each diabetic eats a snack after the fasting blood is drawn and medications are taken. However, in a large study, a few hypoglycemic reactions may still occur. If recognized promptly by clinic staff, they should be mild and easily treated with orange juice or a similar sugar-containing beverage. An additional problem, marked hyperglycemia or uncontrolled diabetes, should be very rare in participants examined by Health ABC.

Hypoglycemia, or an abnormally low blood glucose level, occurs when there is an imbalance between the dose of hypoglycemic medications and the diabetic participant's food intake and activity level. Classic symptoms include anxiety, tremor, palpitations, sweating, faintness, and hunger. If untreated, a further decrease in blood glucose may lead to confusion followed by loss of consciousness. Prolonged hypoglycemia may cause permanent brain damage or precipitate angina pectoris or seizures.

It is important to remember that symptoms of hypoglycemia are variable and may be partially masked in elderly participants.

If a diabetic displays any of these symptoms and is able to take food orally, orange juice containing additional sugar should be given immediately. This should be sufficient to treat most hypoglycemic reactions. If a diabetic loses consciousness, hypoglycemia should be presumed until ruled out. Severe hypoglycemic reactions are a medical emergency and should be treated promptly with intramuscular glucagon or intravenous glucose. Clinics should have staff trained to administer one of these emergency therapies. If a comatose participant does not respond promptly, they should be transported immediately to an emergency care facility. If a severe hypoglycemic reaction occurs, the diabetic should be evaluated by medical staff prior to returning home.

4. Participant Preparation

All participants are asked to come to the clinic in the morning after a 12-hour fast. The overnight fast will be explained at the home visit when scheduling for the clinic visit.

Clinic staff should reassure the participants that the OGTT is safe and has few, if any, side effects. There are many misconceptions regarding the OGTT. Until a few years ago, larger doses of glucose were commonly administered and some patients complained about the fluid volume and/or subsequent GI distress. During the last ten years, a lower dose of glucose has greatly reduced this problem. In a study performed by the National Institute of Aging, only 0.3% (3 per thousand) participants complained of side effects, all of which were mild and transient. No significant problems were encountered in those over 75 years of age. Because some participants may have heard that this test is uncomfortable, it is important to reassure them that this test should cause them no discomfort. If participants complain of any problems during the test, this should be recorded in the participant's folder.

5. Detailed Measurement Procedures

5.1 General Issues

All participants except diabetics treated with insulin or oral hypoglycemics will have the glucose tolerance test.

Fasting blood samples in all participants, including diabetics, are drawn soon after arrival in the clinic (ECG must be done first).

In most cases, the phlebotomist who did the fasting blood draw will administer the glucose drink.

Diabetics on insulin or hypoglycemic medications should take their medication and have a snack.

5.2 Administration

5.2.1 Explanation of the Test and Final Eligibility Determination

1) If the patient is not known to have diabetes and is being administered the OGTT the following should be said:

Script: “The test you are about to take is a test to see if you have diabetes. If you have diabetes, your blood sugar levels rise because of the foods you eat.”

“You have been fasting for 12 hours. The first part of the test will be to test the sugar in the blood that was just drawn. Then we will ask you to drink a liquid that has sugar in it. After two hours, another sample of blood will be taken. We will compare the sugar in your blood before and after you drank the liquid.”

“This test is safe and should not cause you any discomfort. A study performed by the National Institute of Aging found that only 1 person in 3,000 had very mild discomfort from this test.”

2) If the patient has diabetes but is not required to take hypoglycemic medications, the following is said:

Script: “As you probably know, when you have diabetes your blood sugar rises because of the foods you eat. You have been fasting for 12 hours. The first part of the test will be to test the sugar in the blood that was just drawn. Then we will ask you to drink a liquid that has sugar in it. After two hours, another sample of blood will be taken. We will compare the sugar in your blood before and after you drank the liquid.”

“This test is safe in people who have diabetes and should not cause you any discomfort. A study performed by the National Institute of Aging found that only 1 person in 3,000 had very mild discomfort from this test.”

The following is asked of all participants at the initial blood draw (see Blood and Urine Collection chapter):

Script: “What is the date and time that you last ate or drank anything other than water?”

This information is recorded on the Phlebotomy form (Questions 9a and 9b). Calculate the number of hours the participant has been fasting, and write this on the Phlebotomy Form (Question 9c). Round down to the nearest full hour. If the participant gives a time that is at least 8 hours before the current time, they are eligible.

5.2.2 Test Procedures and Instructions for Completing the Form

- 1) If a participant is not administered the oral glucose tolerance test, an OGTT form must still be filled out through question 2. In addition, you must put an X in the box labeled N/A next to cryovial 46 on the Laboratory Processing form (see Lab Specimen Processing chapter). *If the participant takes insulin, also put an X in the box labeled N/A next to cryovial 26 on the Laboratory Processing form.*
- 2) All eligible participants receive a standard 75 gram glucose load as a flavored drink (approximately 7 ounces). They receive this drink within 5 minutes of completing their initial blood draw. Record the time of the blood draw on the form. The glucose drink should be consumed in its entirety in 10 minutes or less.
- 3) Timing for the test begins as soon as the participant starts to drink the glucose solution.
- 4) Record whether the participant consumed the entire drink and the time of the start of consumption. Add two hours, and record this time under "Time blood draw due" on the OGTT form.
- 5) If the full contents of the test drink are not consumed, a note should be made in the participant form.
- 6) If the participant drinks less than half of the drink, the test is canceled and no 2-hour blood draw is performed. Put an X in the box labeled N/A next to cryovial 46 on the Laboratory Processing form.
- 7) Two hours after the start of the test, the 2-hour blood sample is obtained for measurement of glucose. The blood sample should be drawn as close to the 2-hour time as possible.
- 8) If blood cannot be obtained within 10 minutes of the scheduled time, the sample should still be drawn.
- 9) Record the time the sample was obtained on the form (Question 5)

5.2.3 Post Glucose Consumption Phlebotomy Scheduling

- 1) Every scheduling effort should be made to allow participants to go to the phlebotomy station for the 2-hour blood sample. In a complex study such as Health ABC, it is inevitable that some participants will be having other parts of the

examination. Adjustments will be necessary as staff gain expertise at each Field Center.

- 2) If the 2-hour blood sample is due and the participant cannot come to the phlebotomy room, the phlebotomist should go to the participant, if possible, to obtain this sample. A note should be made whenever this is necessary. Clinic staff must make this decision, taking into account the safety and comfort of the participants.

5.2.4 Procedure for Return Visit Oral Glucose Tolerance Test

If during the baseline clinic visit the participant has not fasted for at least 8 hours, they will be asked if they would be willing to come back to the clinic fasting at a later date. The procedures for performing the glucose tolerance test are exactly the same for the return visit. The only difference is that no archived blood is drawn, and special forms have been created for recording the procedure. These forms are almost the same as the forms used during the baseline clinic visit and include the Return Visit Lab Collection Form, the Return Visit Oral Glucose Tolerance Form, and the Return Visit Lab Processing Form. Note that the header must be filled out on each of these three forms to include the participant's Health ABC ID #, Acrostic, Date Form Completed, and Staff ID#.

6. Procedures for Performing the Measurement at Home

Not applicable.

7. Alert Values/Follow-up/Reporting to Participants

Fasting Blood Sugar

normal	≤50 mg/dl <115 mg/dl
borderline	115-139 mg/dl
elevated	≥140 mg/dl
immediate alert	>350 mg/dl <50 mg/dl

Two-hour OGTT

normal	≤50 mg/dl <140 mg/dl
borderline	140-199 mg/dl
elevated	≥200 mg/dl
immediate alert	>500 mg/dl <50 mg/dl

Immediate alerts: Notify participant and participant's physician by telephone/fax if participant has granted permission to notify physician. See Appendix 2 for model letter with abnormal lab value filled in.

Elevated values: Notify participant and participant's physician by fax/letter if participant has granted permission to notify physician. See Appendix 2 for model letter with abnormal lab value filled in.

Borderline or normal values: Include in final reports to participant and participant's physician within 8 weeks of clinic visit. Present individual results and normal ranges as above.

Hyperglycemia

Hyperglycemia, an abnormally high blood glucose level, occurs when diabetes is not adequately controlled. In general, unusually high glucose levels will be reported to the Field Centers from the Central Blood Analysis Laboratory and dealt with according to notification protocols above. It is unlikely, but possible, that a diabetic will present for examination with very poor diabetic control. Any diabetic participant complaining of persistent thirst, or who appears visibly short of breath or confused, should be referred for further evaluation since these could be indicative of more severe complications of diabetes requiring prompt medical treatment.

8. Quality Assurance

8.1 Training Requirements

- Read and study manual
- Attend Health ABC training session on techniques (or observe administration by experienced examiner)
- Discuss problems or questions with local expert or QC officer.
- Complete certification exercises.

8.2 Certification Requirements

- Complete training requirements
- Conduct procedure while being observed by QC officer using QC checklist.

Quality Assurance Checklist

- ☐ Fasting status confirmed.
- ☐ Hours fasting recorded on Phlebotomy form.
- ☐ Diabetic status confirmed.
- ☐ Non-fasting and diabetic participants taking insulin or hypoglycemic agents are excluded.
- ☐ N/A box for cryovial 26 checked on Lab Processing form, if participant taking insulin
- ☐ Test not performed if no blood obtained or less than 1/2 of glucose drink consumed.
- ☐ N/A box for cryovial 46 checked on Lab Processing form, if OGTT not administered
- ☐ Time between fasting blood draw and administration of glucose drink recorded
- ☐ Glucose drink given to participant within 5 minutes of blood draw.
- ☐ Glucose dose consumed promptly (within 10 minutes) after given to participant.
- ☐ Time of start of consumption recorded and projected time for 2-hour draw recorded
- ☐ Two-hour blood sample obtained within time limit (± 10 minutes).
- ☐ Reviews form for completeness

9. References

1. Brownlee M, Cerami A, Vlassara H: Advanced glycosylation end products in tissue and the biomechanical basis of diabetic complications. *New Engl J Med* 1988;318:1315-1321.
2. Davidson MB, Peters AL, Schriger DL: An alternative approach to the diagnosis of diabetes with a review of the literature. *Diabetes Care* 1995;18:1065-1071.
3. Hanson RL, Nelson RG, McCance DR, Beart JA, Charles MA, Pettitt DJ, Knowler WC: Comparison of screening tests for non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1993;153:2133-2140.

4. Harris MI, Hadden WC, Knowler WC, Bennett PH: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in US population aged 20-74 years. *Diabetes* 1987;36:523-534.
5. McCance DR, Hanson RL, Charles MA, Lennart T, Jacobsson H, Pettitt DJ, Bennett PH, Knowler WC: Comparison of tests for glycated haemoglobin and fasting and two-hour plasma glucose concentrations as diagnostic methods for diabetes. *BMJ* 1994;308:1323-1328.
6. McCance DR, Hanson RL, Charles MA, Lennart T, Jacobsson H, Pettitt DJ, Bennett PH, Knowler WC: Which test for diagnosing diabetes? *Diabetes Care* 1995;18:1042-1044.
7. Reaven GM, Chen N, Hollenbeck C, Chen YD: Effect of age on glucose tolerance and glucose uptake in healthy individuals. *J Am Geriatr Soc* 1989;37:735-740.
8. Savage PJ, Wahl PW, Tracy RP, Borhani NO, Ettinger WH, O'Leary DH, Gardin JM, Rock R: High prevalence of diabetes and impaired glucose tolerance and their association with elevated insulin levels in elderly women and men: The Cardiovascular Health Study. (submitted for publication)
9. Stolk RP, Orchard TJ, Grobbee DE: Why use the oral glucose tolerance test? *Diabetes Care* 1995;18:1045-1049.
10. WHO. Diabetes mellitus: Report of a WHO study group. WHO Technical Report Series, NO. 727. Geneva: WHO, 1985.

10. Form

APPENDIX 1**The Diagnosis of Diabetes Mellitus: The National Diabetes Data Group Criteria*****Non-Pregnant Adults**

“Unequivocal elevation of plasma glucose concentration together with the classic symptoms of diabetes.” Both criteria are left undefined.[†] Fasting plasma glucose less than 115 mg/dL (6.38 mmol/L) is considered definitely normal.

“Elevated fasting plasma glucose concentration on more than one occasion”; that is, fasting plasma glucose of 140 mg/dL (7.77 mmol/L) or greater.”

“Elevated plasma glucose concentration after an oral glucose challenge on more than one occasion.” Both the 2-hour plasma or serum and some other sample before 2 hours post-glucose must equal or exceed 200 mg/dL (11.1 mmol/L).

Impaired glucose tolerance is diagnosed when the fasting plasma glucose is less than 140 mg/dL and the oral glucose tolerance test 2-hour plasma glucose is between 140 mg/dL and 200 mg/dL and an oral glucose tolerance test plasma glucose prior to 2 hours equals or exceeds 200 mg/dL.

Standards for the oral glucose tolerance test:

The dose is 75 g oral glucose consumed over 5 minutes.

The patient should remain seated throughout the test.

The test should be done in the morning after a 10 to 16 hour fast, preceded by 3 days of a diet containing at least 150 g of carbohydrate, and unrestricted physical activity.

Gestational Diabetes

Diabetes first appearing during pregnancy diagnosed by two or more of the following values after a 100 g oral glucose challenge:

Fasting plasma glucose \geq 105 mg/dL (5.82 mmol/L)

1 hour plasma glucose \geq 190/dL (10.5 mmol/L)

2 hour plasma glucose \geq 165/dL (9.15 mmol/L)

3 hour plasma glucose \geq 145/dL (8.04 mmol/L)

There is no official category of gestational impaired glucose tolerance.

*The diagnosis of diabetes can be unambiguously made only when other physiologic stresses or drugs that produce hyperglycemia are not present.

[†]The World Health Organization defines unequivocal elevation of plasma glucose as at least 140 mg/dL for a fasting specimen or any plasma glucose of at least 200 mg/dL

Reference:

National Diabetes Data Group Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28: 1039-1057.

APPENDIX 2
OGTT ALERT LETTER FOR PHYSICIAN

March 13, 1997

Abe Friedman, M.D.
5845 Centre Avenue
Pittsburgh, PA 15213

Dear Dr. Friedman:

On June 1, 1997, we performed a surveillance visit on your patient _____ at the Health ABC Clinic. [A fasting and 2-hour OGTT glucose were obtained and the results of the fasting glucose are 76 mg/dl, and the 2-hour glucose was 40 mg/dl. (Alert values are <50 mg/dl or >500 mg/dl.)] We will send the remainder of the results when we receive them from the Health ABC Coordinating Center.

All tests were performed for research purposes only and will be used to describe the health status of men and women in their seventies who are taking part in this study. These tests are not intended to replace any tests that might be ordered for a specific clinical indication. Although we do not suggest specific diagnosis or treatment, we hope this information is useful to you and your patient.

If you have any questions, please feel free to contact us at _____. Thank you for your support.

Sincerely,

Anne Newman, M.D., MPH
Health ABC Principal Investigator

Marguerite Meyer, RN, MEd
Coordinator of Clinical Studies

/sa